REMARKS

I. Status of the claims

Claims 1 and 5-30 are pending in the application and stand rejected. Claims 1, 5, 25 and 27 have been amended. Claims 2-4 have been canceled herewith. Applicants thank the Examiner for the helpful discussion of the pending claims and cited references during the in person interview on November 19, 2007.

II. Claim Amendments

Claims 1 and 25 have been amended to recite that the liposomal/complexed antiinfective has a lipid to drug ratio of 2.5:1 or less. Support for this amendment can be found in the specification at page 12, ll. 49-50, and in examples summarized in the table on page 20. Claims 1 and 25 have also been amended to recite that the antiinfective is an aminoglycoside. Support for this amendment can be found, for example, in claim 4 as originally filed and the specification at paragraphs 16 and 17. Claims 1 and 25 have further been amended to recite that the dosing is during a 14-day treatment period. Support for this amendment can be found in the specification at paragraph 22, which explains that an effective amount of drug reduces the CFU count in the lungs by one order of magnitude over the course of a 14 day treatment. Additionally, in the example described at paragraph 61, liposomal/complexed amikacin was administered every other day for 14 days. Claims 1, 25 and 27 have been amended to more clearly describe the invention by replacing the phrase "every week" with "once a week" No new matter has been added by these amendments.

Claims 2-4 have been canceled, and claim 5 has been amended to depend from claim 1 instead of claim 4.

III. Rejections Under 35 U.S.C. § 102(b)

A. Deol

The Examiner has rejected claims 1-2, 17, 18, 21-26, 28 and 30 as being allegedly unpatentable over Deol et al. "Lung specific stealth liposomes: stability, biodistribution and toxicity of liposomal antitubercular drugs in mice," Biochimica et Biophysica Acta 1334 (1997) 161-172 ("Deol"). The Examiner states that the "Deol teaches the treatment of tuberculosis in mice by the administration of liposomal formulations containing ant[i] tubercular drugs rifampicin and isoniazid. the liposomes contain cholesterol and the administration is once." *Office Action* at p. 2. Applicants respectfully traverse.

To anticipate a claim under §102(b), a reference must teach each and every element of the claim, either expressly or inherently. M.P.E.P. § 2131. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union oil Co. of* California, 8144. F. 2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Furthermore, "[t]he identical invention must be shown in as complete detail as contained in the . . . claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1566 (Fed. Cir. 1990).

Claim 1 as currently amended recites a method of "treating pulmonary infection in a patient comprising pulmonary administration of an effective amount of a liposomal/complexed antiinfective to the patient, wherein the (i) administrated amount is 50% or less of the comparative free drug amount, or (ii) the dosing is from once a day to once a week during a 14-day treatment period, or (iii) both; wherein the liposomal/complexed antiinfective comprises at least one sterol; wherein the antiinfective is an aminoglycoside, and wherein the liposomal/complexed antiinfective

has a lipid to drug ratio of less than 2.5:1." Applicants submit that Deol does not disclose a liposomal/complexed aminoglycoside, but rather discloses only isoniazid and rifampicin. Deol also does not disclose dosing from once a day to once a week over a 14 day treatment period, 50% or less of the administered amount, or a lipid to ratio of 2.5 or less. Additionally, Deol does not disclose pulmonary administration of its liposome, but rather discloses only intravenous administration. *Deol* at abstract, p. 161 and p. 163. For at least these reasons, Deol does not anticipate the present claims. Applicants respectfully request withdrawal of this rejection.

B. Hersch

The Examiner also has rejected claims 1-4, 6, 17, 18, 21-26, 28 and 30 as allegedly anticipated by U.S. Patent No. 5,756,120 to Hersch et al. ("Hersch"). Specifically, the Examiner states that "Hersch teaches liposomal formulations containing amino glycosides for the infections caused by Pseudomonas, M. avium and M. tuberculosis." *Office Action* at p. 3. Applicants respectfully traverse.

Hersch describes liposomes containing a neutral lipid, a phosphatidyl glycerol, cholesterol, and amikacin, *Hersch* at col. 5, ll. 52-55, where the drug to total lipid ratio is from 1:9 to 1:3. Hersch does not disclose a lipid to drug ratio of 1:2.5. or less, as recited in the pending claims. Hersch also does not disclose that the "administrated amount is 50% or less of the comparative free drug amount," or that "the dosing is from once a day to once a week during a 14-day treatment period." Finally, Hersch does not disclose pulmonary administration of its formulation. For at least these reasons, Applicants submit that Hersch does not anticipate the present claims. Withdrawal of this rejection is respectfully requested.

IV. Rejections Under 35 U.S.C. § 103(a)

A. Hersch

The Examiner has rejected claims 1-30 as allegedly obvious over Hersch. According to the Examiner, Hersch "teaches liposomal formulations containing amino glycosides for the treatment of the infections caused by Pseudomonas, M. avium and M. tuberculosis." *Office Action* at p. 3. The Examiner notes that "[w]hat is lacking in Hersch is the claimed protocol of administration as claimed in the instant claims." The Examiner contends that "whether the composition has to be administered daily or once a day and the dosage depend upon the severity of the condition, the age of the patient and other parameters, they are deemed to be obvious parameters manipulated by an artisan to obtain the best possible results." *Id.*

In order to establish a *prima facie* case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 (1966). Once the Graham factual inquiries have been resolved, the Examiner must explain why the differences between the cited references and the claims would have been obvious to one of ordinary skill in the art. Fed. Reg. Vol. 72, No. 195, p. 57527. The Supreme Court in *KSR* stressed that "obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* 127 S.Ct. 1727, 1740 (2007); see also Fed. Reg. Vol. 72, No. 195, p. 57529. "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. Fed. Reg. Vol. 72, No. 195 at p. 57528. Applicants respectfully submit the rejection over Hersch fails to meet this standard.

As explained above, Hersch fails to teach a lipid to drug ratio of 1:2.5 or less. Hersch also does not disclose that the "administrated amount is 50% or less of the comparative free drug amount," that "the dosing is from once a day to once a week during a 14-day treatment period," or pulmonary administration of its formulation. Applicants further submit that Hersch fails to render these missing elements obvious.

In particular, Applicants submit that the present dosing is not merely an obvious parameter based on factors such as age of the patient. In present composition, the less frequent, e.g. once a day, and lower dosing can be achieved, at least in part, because of the liposomal formulation properties. For example, the low lipid to drug ratio reduces the total amount of the formulation that must be administered, while the sterol present in the liposome provides a slower drug release profile. Notably, Hersch fails to teach or suggest any liposomal formulations having the presently claimed lipid/drug ratio, and further fails to provide any method for producing such a formulation. Hersch also notably lacks any teaching or suggestion to administer its formulation from once a day to once a week for a 14-day treatment period via any route of administration, much less pulmonary administration as claimed.

Indeed, the skilled artisan would have no reasonable expectation of success in administering an aminoglycoside via inhalation using the presently claimed method because the skilled artisan would recognize the risk of drug resistance that would result from such a reduction. In contrast, Applicants have demonstrated that the formulation recited in the claims, having at least one sterol, releases the antiinfective much more slowly than the free drug, thus providing higher antiinfective levels in the lung over a longer period of time. (*See Specification*, Figs. 2-7.) In particular, the example described at paragraphs 61 demonstrates the slow release and sustained antiinfective

capabilities of a liposomal/complexed aminoglycoside using pulmonary administration once every other day.

Applicants further submit that the Examiner's broad statement that one of skill in the art would consider the protocol of administration "obvious parameters manipulated by an artisan to obtain the best possible results" is merely conclusory, and fails to meet the standard required by the Patent Office guidelines. As discussed above, "obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* 127 S.Ct. at 1740; Fed. Reg. Vol. 72, No. 195, p. 57529. A general goal to "achieve the best possible results" hardly provides an articulated reason or rational underpinning. For at least this reason, Applicants submit that the Examiner has failed to establish a prima facie case of obviousness.

For all of the aforementioned reasons, Applicants respectfully request withdrawal of this rejection.

B. Gonda

Claims 1-30 stand rejected as being allegedly obvious over U.S. Publication No. 2005/0019926 to Gonda et al. ("Gonda"). The Examiner contends that Gonda discloses "liposomal formulations containing amino glycosides," and that these formulations "can be used for treatment of bacterial diseases in cystic fibrosis patients." *Office Action* at p. 4. The Examiner acknowledges that Gonda does not disclosed the "claimed protocol of administration," but again contends that "whether the composition has to be administered daily or once a day and the dosage depend upon the severity of the condition, the age of the patient and other parameters," and these are "deemed to

be obvious parameters manipulated by an artisan to obtain the best possible results." *Id.* Applicants respectfully traverse.

Gonda provides no teaching with respect to the lipid/drug ratio of the nucleic acid-aminoglycoside complex. Thus, Gonda is missing the present claim element of a lipid to drug ratio of 1:2.5 or less.

Gonda, like Hersch, also notably lacks any teaching or suggestion to administer its formulation according to the presently claimed method. As explained with respect to Hersch, the skilled artisan would have no reasonable expectation of success in administering an aminoglycoside via inhalation using the presently claimed method because the skilled artisan would recognize the risk of drug resistance that would result from such a reduction. In contrast, Applicants have demonstrated that the formulation recited in the claims, having at least one sterol, releases the antiinfective much more slowly than the free drug, thus providing higher antiinfective levels in the lung over a longer period of time. (*See Specification*, Figs. 2-7.) In particular, the example described at paragraphs 61 demonstrates the slow release and sustained antiinfective capabilities of a liposomal/complexed aminoglycoside using pulmonary administration once every other day.

As explained with respect to Hersch, Applicants the Examiner's broad statement that one of skill in the art would consider the protocol of administration "obvious parameters manipulated by an artisan to obtain the best possible results" is merely conclusory, and fails to meet the standard required by the Patent Office guidelines. As discussed above, "obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* 127 S.Ct. at 1740; Fed. Reg.

Vol. 72, No. 195, p. 57529. A general goal to "achieve the best possible results" hardly provides an articulated reason or rational underpinning to support and obviousness conclusion

For at least these reasons, Applicants submit that the present claims are not obvious over Gonda.

C. Lagace in view of Deol or vice versa

The Examiner contends that claims 1-30 are unpatentable over U.S. Patent No. 5,662,929 to Lagace et al. ("Lagace") in combination with Deol or vice versa. The Examiner admits that Lagace does not teach "inclusion of cholesterol in the liposomes," nor does Lagace teach "the claimed protocol of administration." *Office Action* at p. 5. The Examiner relies on Deol for teaching "that cholesterol-containing liposomes are more stable." *Id.* Based on these teachings, the Examiner concludes that it would have been obvious to one of ordinary skill in the art.

Lagace describes liposomal formulations containing therapeutic agents, such as antibiotics. *Lagace* abstract. According to Lagace, "in order to maintain the desired characteristic of the liposome formulation, a low rigidity of the liposomes seems required." *Id.* at col. 10, l. 67 to col. 11, l. 5. According to Lagace, an aspect of the invention is "a low rigidity multilamellar liposomal formulation free of cholesterol." *Id.* at column 5, ll. 49-50. Thus, Lagace instructs the skilled artisan not to use cholesterol in the formulation. (*Id.*)

Applicants respectfully remind the Examiner that reference must be considered in its entirety, for all that it teaches. Thus, a reference must be considered as a whole, including disclosures that away from the claimed invention. M.P.E.P. § 2142.02. Under *KSR*, "teaching away" still provides evidence of non-obviousness. *See* 127 S.Ct. at 1745. "[P]roceeding contrary to accepted wisdom in the art is evidence of nonobviousness." M.P.E.P. §2145 (citing *in re Hedges*,

783 F.2d 1083 (Fed. Cir. 1986)). If when combined, the references "would produce a seemingly inoperative device," then they teach away from their combination. *Tec Air, Inc. v. Denso Mfg. Michigan, Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999). *See also, In re Fritch*, 972 F. 2d 1260, 1265 n. 12 (Fed. Cir. 1982) ("A proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose.").

Lagace strongly and repeatedly teaches *against* the use of sterols to form the liposome. Instead, the liposomes of Lagace lack rigidity, thus precluding the claimed dosing schedule of once a day, once every two days, once every third day, or every week. Lagace specifically points out that "the addition of cholesterol to the formulation described in Table 1 brought the Tc to a minimum value of 60° C. Such formulations were incompatible with modulation of gradual antibiotic liberation and suitable interactions with bacteria." *Lagace* at col. 10, ll. 63-66. Thus, Lagace states "in order to maintain the desired characteristic of the liposome formulation, a low rigidity of the liposomes seems required. This low rigidity can be achieved by maintaining a low temperature of phase transition . . . and avoiding the use of cholesterol in the formulation." *Lagace* at col. 10, l. 67 to col. 11, l. 5, emphasis added.

Although Deol describes the use of cholesterol in its formulations, the skilled artisan would not use a sterol based on the teachings of Lagace since the Lagace formulations must not be rigid. Indeed, Lagace expressly teaches that its liposomes would not work for their intended purpose if combined with Deol's teachings to use cholesterol. For Example, Lagace states "the presence of cholesterol in the therapeutic liposomal formulation improves liposome stability in a way that goes against the desired therapeutic activity of the formulation." Thus, Lagace, like Deol, recognizes greater stability of some cholesterol containing liposomes, yet explicitly instructs against their use.

Lagace, like Hersch and Gonda, also lacks any teaching or suggestion to administer its formulation according to the presently claimed method. As explained with respect to Hersch, the skilled artisan would have no reasonable expectation of success in administering an aminoglycoside via inhalation using the presently claimed method because the skilled artisan would recognize the risk of drug resistance that would result from such a reduction. In contrast, Applicants have demonstrated that the formulation recited in the claims, having at least one sterol, releases the antiinfective much more slowly than the free drug, thus providing higher antiinfective levels in the lung over a longer period of time. (*See Specification*, Figs. 2-7.) In particular, the example described at paragraphs 61 demonstrates the slow release and sustained antiinfective capabilities of a liposomal/complexed aminoglycoside using pulmonary administration once every other day.

As explained with respect to Hersch, the Examiner's broad statement that one of skill in the art would consider the protocol of administration "obvious parameters manipulated by an artisan to obtain the best possible results" is merely conclusory, and fails to meet the standard required by the Patent Office guidelines. As discussed above, "obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* 127 S.Ct. at 1740; Fed. Reg. Vol. 72, No. 195, p. 57529. A general goal to "achieve the best possible results" hardly provides an articulated reason or rational underpinning to support and obviousness conclusion

For at least these reasons, Applicants respectfully request withdrawal of this rejection.

The Examiner further contends that it would have been obvious to use aminoglycosides, as taught by Lagace, with the liposomes of Deol because "one would encapsulate any antibiotic to treat a disease causing bacteria." *Office Action* at p. 6. Even if one would use an aminoglycoside in

Deol's liposomal formulation, Deol fails to disclose the lipid/drug ratio as recited in claims 1 and 25, and also fails to disclose pulmonary administration according to the presently claimed method.

Applicants further submit that The examiner statement that one would encapsulate "any antibiotic" in the liposomes of Deol is merely conclusory, and find no support in the reference teachings. If anything, the skilled artisan would have no reasonable expectation of success in using an aminoglycoside in Deol's formulations because of Lagace's strong teachings against using cholesterol in liposomal formulations for encapsulating aminoglycosides.

For at least these reasons, Applicants respectfully request withdrawal of this rejection.

D. Lagace in view of Hersch

The Examiner acknowledges again that Lagace does not disclose inclusion of cholesterol in the liposomes. The Examiner relies Hersch for "show[ing] the routine use of cholesterol in liposomes." *Office Action* at p. 6. Thus, the Examiner concludes that the use of cholesterol in the liposomes of Lagace would have been obvious "since Hersch shows the routine use of cholesterol in liposomes for the treatment of infections." Applicants respectfully traverse.

Lagace in view of Hersch fails to render the instant claims obvious for reasons similar to those regarding Lagace and Deol. As discussed in detail above, Lagace repeatedly instructs against the use of cholesterol in its liposomes.

Furthermore, as discussed with respect to Hersch, Lagace and Gonda, the combination of Lagace with Hersch fails to render the method of pulmonary administration obvious. Again, the skilled artisan would have no reasonable expectation of success in administering an aminoglycoside via inhalation using the presently claimed method because the skilled artisan would recognize the risk of drug resistance that would result from such a reduction. In contrast, Applicants have

demonstrated that the formulation recited in the claims, having at least one sterol, releases the antiinfective much more slowly than the free drug, thus providing higher antiinfective levels in the lung over a longer period of time. (*See Specification*, Figs. 2-7.) In particular, the example described at paragraphs 61 demonstrates the slow release and sustained antiinfective capabilities of a liposomal/complexed aminoglycoside using pulmonary administration once every other day.

As explained above, the Examiner's broad statement that one of skill in the art would consider the protocol of administration "obvious parameters manipulated by an artisan to obtain the best possible results" is merely conclusory. "[O]bviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* 127 S.Ct. at 1740; Fed. Reg. Vol. 72, No. 195, p. 57529. A general goal to "achieve the best possible results" hardly provides an articulated reason or rational underpinning to support and obviousness conclusion

V. Double Patenting

Claims 1-30 stand rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 74-76, 78-84, 86-87, 94-95, 98-102 and 105-108 of copending Application Serial No. 10/383,173 ("the '173 application"), either alone or in combination with Lagace. Applicants respectfully request that the Examiner hold in abeyance all obviousness-type double patenting rejections based on the '173 application until allowable subject matter is indicated.

VI. Conclusion

In light of the amendments and remarks set forth above, Applicants submit that the pending claims are in condition for allowance. Reconsideration and timely allowance of the pending claims

is respectfully solicited. If a telephone conference would be helpful, the Examiner is invited to call the undersigned at 617-832-1223. Applicants hereby request that any additional fees required for timely consideration of this application be charged to **Deposit Account No. 06-1448, Reference TRA-008.01**

Dated: February 11, 2008

Respectfully submitted,

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